A Meta-Analytic Framework for Assessing Surrogate Outcomes

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1. **Estimating the Effects of Treatment on the True Endpoint ,T, from Data on Surrogate Outcomes, S**

2. **Inference for Means (T_{1i} , S_{1i} , T_{2i} , S_{2i})**

3. **Inference for General Parameters**

$$(\hat{\theta}_{1ti}, \hat{\theta}_{1si}, \hat{\theta}_{2ti}, \hat{\theta}_{2si})$$

4. **Problems and Needed Research**

Class of Experiments , C

Parameters $\mu_i = (\mu_{1ti}, \mu_{1si}, \mu_{2ti}, \mu_{2si})^T$

Distribution of μ_i **over** C**:** $N(\mu, \phi)$

Given μ_i**, the quantities** (T_{1i}, S_{1i}) **and** (T_{2i}, S_{2i}) **are**

independent with respective covariances Σ_{11i} **and** Σ_{22i}**.**

These covariances can be estimated from individual-level

data (T_{1ij}, S_{1ij}) $j=1,2,\ldots n_i$ **and** (T_{2ij}, S_{2ij}) $j=1,2,\ldots m_i$

New study, N, from class *C*

We want a prediction interval on $\mu_{1tN} - \mu_{2tN}$.

Given S_{1N}, S_{2N}, $\sigma_{22N} = Var(S_{1N})$ **, and**

$\sigma_{44N} = Var(S_{2N})$, $\mu_{1tN} - \mu_{2tN}$ **is normal with mean**

$m(\theta) =$

$$(\mu_{1t} - \mu_{2t}) + (S_{1N} - \mu_{1s}, S_{2N} - \mu_{2s}) \begin{pmatrix} \sigma_{22N} + \phi_{22} & \phi_{24} \\ \phi_{42} & \sigma_{44N} + \phi_{44} \end{pmatrix}^{-1} \begin{pmatrix} \phi_{12} - \phi_{23} \\ \phi_{14} - \phi_{34} \end{pmatrix}$$

and with variance $V(\theta) =$

$$(\phi_{11} - \phi_{31} - \phi_{13} + \phi_{33}) - (\phi_{12} - \phi_{32}, \phi_{14} - \phi_{34}) \begin{pmatrix} \sigma_{22N} + \phi_{22} & \phi_{24} \\ \phi_{42} & \sigma_{44N} + \phi_{44} \end{pmatrix}^{-1} \begin{pmatrix} \phi_{12} - \phi_{23} \\ \phi_{14} - \phi_{34} \end{pmatrix}.$$

Prediction interval on $\mu_{1tN} - \mu_{2tN}$ **is** $m(\theta) \pm 1.96 V(\theta)^{1/2}$

1. **The precision of this prediction interval is better than that based on the distribution of $\mu_{1tN} - \mu_{2tN}$ given (S_{1N} - S_{2N}).**

   cf Daniels MJ and Hughes MD. Stat Med 16:1965-1982, 1997

2. **The structure above is similar to Buyse, Molenberghs, Burzynski, Renard and Geys (submitted) except that they assume $\Sigma_{11i}=\Sigma_{22i}$.**

3. **Even if n_i and m_i tend to infinity, so that $\Sigma_{11i}=\Sigma_{22i}=0$, the prediction interval has positive width. In contrast, if we had direct data on T_{1N} and T_{2N}, the width of the prediction interval would go to zero.**

There is a need to estimate the parameters $\theta = (\mu, \phi)$.

Suppose we have M previous experiments from class *C*. The unconditional distribution of $\left(T_{1i}, S_{1j}, T_{2i}, S_{2j}\right)^T$ is normal with mean μ and covariance

$$\begin{pmatrix} \sigma_{11i}+\phi_{11} & \sigma_{12i}+\phi_{12} & \phi_{13} & \phi_{14} \\ \sigma_{21i}+\phi_{21} & \sigma_{22i}+\phi_{22} & \phi_{23} & \phi_{24} \\ \phi_{31} & \phi_{32} & \sigma_{33i}+\phi_{33} & \sigma_{34i}+\phi_{34} \\ \phi_{41} & \phi_{42} & \sigma_{43i}+\phi_{43} & \sigma_{44i}+\phi_{44} \end{pmatrix}.$$

Pseudo-maximum likelihood (empirical Bayes) maximizes over μ and ϕ with elements of $\hat{\Sigma}_{11i}$ and $\hat{\Sigma}_{22i}$ inserted.

To correct the prediction interval for using estimates of parameters, bootstrap to find the constant c_α such that

$$E_{\hat{\theta}}\left\{\Phi(m(\hat{\theta})+c_\alpha V(\hat{\theta})^{1/2})-\Phi(m(\hat{\theta})-c_\alpha V(\hat{\theta})^{1/2})\right\}=1-\alpha$$

Carroll, RJ and Rupert, D. Technometrics, 33:197-210, 1991.

Laird, NM and Louis, TA. JASA 82:739757, 1987

Generalization : $\hat{\theta}_i = (\hat{\theta}_{1ti}, \hat{\theta}_{1si}, \hat{\theta}_{2ti}, \hat{\theta}_{2si})$ **estimates the parameters (of interest) of the marginal distributions** $F(t|\theta_{1ti}), F(s|\theta_{1si}), F(t|\theta_{2ti}), F(s|\theta_{2si})$.

Components of $\hat{\theta}_i$ **are solutions to score equations.**

Suppose $\theta_i = E(\hat{\theta}_i)$ **is normally distributed,** $N(\theta, \phi)$.

Given θ_i, $(\hat{\theta}_{1ti}, \hat{\theta}_{1si})$ **and** $(\hat{\theta}_{2ti}, \hat{\theta}_{2si})$ **are independent with respective covariances** Σ_{11i} **and** Σ_{22i}. **These covariances can be estimated from individual-level data using a sandwich estimate based on the empirical covariances of the score equations.**

Issues/Questions

1. **How do you define the class *C*?**

2. **Can you get individual-level data on a sufficient number of antecedent studies to estimate distribution over *C* reliably?**

3. **Will there be sufficient precision in the prediction interval on $\mu_{1tN} - \mu_{2tN}$, even with a very large experiment and precise estimates of S_{1N} and S_{2N}? This depends on ϕ.**

4. **Is the analysis sensitive to the assumption that μ_i is normally distributed? If so, how can one test violations of this assumption? Can one reparameterize to parameters that are plausibly jointly normal? Can one**

use Markov Chain Monte Carlo methods for non-normal "priors" on μ_i?

5. What about toxicity that is not encompassed in the main clinical endpoint, T?